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REMARKS

Reconsideration of this application is respectfully requested. Claims 46-48 and 62 have been cancelled in this amendment. Claims 16, 25, 34, 40, 41, and 58 are currently pending. New claims 63-65 have been added and are supported by original claims 46, 48, and 19, respectively. These new claims do not add new matter.

In item 2 of the Office Action dated January 28, 2004, the Office noted that copies of the references cited in the Information Disclosure Statement and Form 1449 had not been received. Applicants have attached a copy of the stamped postcard, dated June 12, 2003, indicating that seven references were filed. To further prosecution, Applicants submit additional copies of these references herewith and respectfully request that the Form 1449 reflect that they were considered.

In item 13, the Office maintained the rejection of claims 16, 25, 34, 40-41, 46-48, 58, and 62 under 35 U.S.C. § 101, because it asserted that the claimed invention lacks a credible or well established utility. Applicants' cancellation of claims 46-48 and 62 obviates this rejection for these claims.

Applicants previously traversed this rejection by noting the utility of the invention, but the Office did not accept Applicants' argument, asserting instead that Applicants cited only "general 'developmental defects' in mutant embryos, as well as general methods where one skilled in the art is invited to discover the function of Nap1/2 [sic]." Office Action of January 28, 2004, at 4. Furthermore, the Office repeated its argument that

> no specific utility exists for the instant claimed gene sequences, because no **specific** biological activity nor specific "developmental defect" is described within the specification that is specifically associated with any nucleic

> acid transcribed by the promoter polynucleotide sequence of SEQ ID NO: 4.

Id. Despite the Office's characterization of the experiments described in the Specification, the Specification contains much evidence of the **specific** biological activity and **specific** developmental events of the polynucleotide sequence of SEQ ID NO: 4.

As Applicants previously explained, deletion of the *Nap1l2* gene, the mouse homologue of the gene, which is under the control of the polynucleotide sequence in SEQ ID NO: 4, in mouse embryonic stem cells that have the potential to become a developing embryo, demonstrates the specific biological activity of the polynucleotide. When these embryonic stem cells were aggregated with morulas, which are balls of normal embryonic cells at a stage of development similar to the embryonic stem cells, the resulting embryos that survived after 9.5 days exhibited specific defects because of the deleted *Nap1l2* gene. The observed defects were mostly of the developing neural system, in particular the neural tube, which is one of the first, fundamental embryonic structures and serves as the precursor for the brain and spinal chord. To proceed with normal development, the neural tube must close completely, but in the embryos with the mutated *Nap1l2* gene, neural tube closure was not complete. In addition, there was a marked overproduction of the cell types that form the neural tube, called the surface ectoderm. *See* Specification at 3, lines 10-18.

This biological activity was characterized in the Specification, with the following description: "Taken together, these results suggest that the absence of *Nap1l2* function leads to an overproduction of cells in the neural tube and the surface ectoderm, and that this interferes with the proper histogenesis of these tissues." *Id.* at 53, lines 12-15.

Furthermore, Figures 5 and 6 depict embryos that have the *Nap1l2* gene deleted and display other specific defects. These defects include anencephaly, an absence of all or part of the brain, and a detached surface ectoderm, the outer layer of the embryonic cells. In addition, an open neural tube was observed in the upper region of some of the embryos. Embryos with significant rearrangements of the regions of the developing brain, exposed neural tubes and tissue, detached spinal chords, overproduction of surface ectoderm, and necrosis, or cell death, in the brains were also observed. Each of these defects was the result of the absence of a functional *Nap1l2* gene in this controlled study. *See* Specification at 12, line 19 through pg. 14, line 4.

Therefore, despite the Office's assertion that these are "general 'developmental defects'", Office Action at 4, Applicants have provided abundant details of the function and the **specific** biological activity of the gene *Nap1l2*, and therefore the *NAP1L2* gene and its control by SEQ ID NO: 4.

The specific biological activity of SEQ ID NO: 4 in controlling expression of the *NAP1L2* gene to prevent the overproduction of cells in the neural tube and the surface ectoderm, highlights the utility presented by the claimed invention. For instance, the polynucleotides can be modified and used to develop embryos that lack functional *Nap1l2* genes and display the specific defects shown. *See* Specification at 56, lines 5-10. Such mutant embryos are then useful in screening methods to identify therapeutic compounds that alter or prevent developmental defects, such as spina bifida or anencephaly. *See* Specification at 9, lines 12-20. In addition, the claimed polynucleotide of the invention is useful in diagnostic screening methods to detect neural system defects. *See* Specification at 4, line 22, through page 5, line 5.

The Office has compared the evidence of utility of this claimed invention to that in *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966). In contrast to the situation in *Manson*, Applicants have provided concrete evidence of utility for their claimed invention, and therefore have distinguished their claims from those in *Manson*. Manson endeavored to show utility in a claimed process for producing a chemical compound by showing that a *closely related* chemical compound had tumor inhibiting effects in mice. *See id.* at 690. Manson did not provide direct evidence of a utility, but rather evidence by the analogy of one compound to another. The Court noted that this evidence "did not disclose a sufficient likelihood that the steroid yielded by his process would have similar tumor-inhibiting characteristics." *Id.* at 694. Therefore, the Court found that the utility requirement had not been met.

In contrast, Applicants' evidence of utility is direct and is not simply an analogy to another compound. Applicants have shown that mice lacking a gene under the control of a polynucleotide that is the mouse homologue of the claimed polynucleotide demonstrate the specific biological activity of overproduction of specific cells in the neural tube and the surface ectoderm. These effects are not those of a similar polynucleotide, but are the actual effects of the polynucleotide of the claimed invention. There is no need for one of skill in the art to "hunt" for the utility of the invention, as the Court characterized the situation in *Manson*, *see id.* at 696, because the specific biological activity of the claimed polynucleotide is provided in the Specification.

In light of the specific biological activity and therefore the utility of the invention, Applicants respectfully request that the rejection under 35 U.S.C. § 101 be withdrawn.

The Office used the rationale of a lack of utility to reject claims 16, 25, 34, 40-41, 46-48, 58, and 62 under 35 U.S.C. § 112, first paragraph, because it asserted that one of skill in the art would not know how to use the claimed invention without a credible utility. *See* Office Action of January 28, 2004 at item 14. Applicants have canceled claims 46-48 and 62, and so have obviated this rejection of those claims. In regard to claims 16, 25, 40-41, 58, and new claims 63-65, as discussed above, the invention has a credible utility in assays, such as diagnostic screening methods and screening methods to identify therapeutic compounds that alter or prevent developmental defects, such as spina bifida, anencephaly, or other defects resulting from the overproduction of neural tube and surface ectoderm cells. Therefore, one of skill in the art would know how to use the invention, and Applicants respectfully request that the rejection be withdrawn.

In item 15, the Office rejected claims 40-41, 46-48, 58, and 62 under 35 U.S.C. § 112, first paragraph, because of the term "high stringency." Applicants have canceled claims 46-48 and 62 and have thus obviated this rejection. In addition, merely to further prosecution, Applicants have deleted the term "high stringency" from claim 40, from which claim 58 depends. Accordingly, Applicants respectfully request that the rejection be withdrawn.

The Office also noted that the specification had not been amended to reflect the sequences present in the deposited plasmids listed on page 44 and in the Deposit Declaration filed with the previous Amendment. Applicants note that the claimed plasmids are clearly identified by the name of the depository and the corresponding accession numbers, and are publicly available. Because no further information is

required to identify the claimed plasmids, Applicants chose not to amend the specification and request that any rejection based on the Office's comment be withdrawn.

In item 16, the Office rejected claims 16, 25, 34, 40, 46-48, 58, and 62 under 35 U.S.C. § 112, first paragraph, as not being enabled for fragments of SEQ ID NO: 4, which provide a promoter function. Applicants have canceled claims 46-48 and 62, and thus have obviated this rejection of these claims. Furthermore, merely to further prosecution, Applicants have deleted the language "or a fragment thereof having a promoter function" from claims 16 and 25, thus obviating the rejection of these claims and claims that depend on them. Finally, Applicants note that, as discussed above, claim 40 has also been amended, merely to further prosecution, to remove a claim term referring to "high stringency", and therefore does not recite a sequence that is characterized by hybridization. Applicants respectfully request that this rejection under 35 U.S.C. § 112 be withdrawn.

In item 17, the Office rejected claims 46-48 and 58 for failing to particularly point out and distinctly claim the invention, as required in 35 U.S.C. § 112, second paragraph, because it asserted that the term "operably linked to SEQ ID NO: 4" is ambiguous and contradictory. Applicants have canceled claims 46-48, and claim 58 no longer depends from claim 48, but from claim 40, which does not recite the phrase "operably linked." Accordingly, the basis for this rejection has been obviated and Applicants request that the rejection be withdrawn.

In item 18, the Office rejected claims 40 and 62 as being anticipated under 35 U.S.C. § 102(b) by Adams et al. because the sequence disclosed in Adams et al. is

96.9% identical to SEQ ID NO: 4. Applicants have canceled claim 62 and have amended claim 40 so that it no longer claims a sequence that hybridizes to SEQ ID NO: 4. Therefore, because the sequence disclosed in Adams et al. does not recite the identical sequence as claimed in claim 40, Applicants respectfully request that the rejection of this claim be withdrawn.

In item 19, the Office rejected claims 40, 46, 47, and 62 under 35 U.S.C. § 102(b) as being anticipated by Chen et al. because of the claim language "comprising . . . a gene sequence." Applicants have canceled claims 46 and 47, obviating the rejection for these claims. Merely to further prosecution, Applicants have amended claim 40 so that the gene sequence claimed "*consists* of the insert contained in the plasmid pBX1 (SEQ ID NO: 4)". Because Chen et al. discloses a sequence that is 153,578 bases long, whereas SEQ ID NO: 4 is only 1,520 bases long, Chen et al. does not anticipate the polynucleotide claimed in claim 40, or in claim 58, which depends from claim 40. Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) in light of Chen et al. be withdrawn.

Applicants respectfully request that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, placing claims 16, 25, 34, 40, 41, 58, and 63-65 in condition for allowance. Applicants submit that the proposed amendments of these claims do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner, since all of the elements and their relationships claimed were present in the earlier claims examined. Therefore, this Amendment should allow for immediate action by the Examiner.

Finally, Applicants submit that the entry of the Amendment would place the application in better form for appeal, should the Examiner dispute the patentability of the pending claims.

Applicants therefore request the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
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Dated: May 18, 2004

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Attachments: Copy of stamped postcard dated June 12, 2003
Copies of seven references submitted on June 12, 2003

PLEASE STAMP TO ACKNOWLEDGE RECEIPT OF THE FOLLOWING:

In Re Application of: Ute ROGNER, et al.

Application No.: 09/847,665 Group Art Unit: 1647

Filed: May 3, 2001 Examiner: Hayes, R.C.

For: IDENTIFICATION OF NEURAL DEFECTS ASSOCIATED WITH THE NUCLEOSOMAL ASSEMBLY PROTEIN 112 GENE

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1. Information Disclosure Statement (2 pgs.)
2. PTO Form 1449 (1 pg.)
3. Copies of 7 references

Dated June 12, 2003

Docket No.: 03495-0203-00000

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(Due Date: June 12, 2003)